ER Management of Depression for PGY1s

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DepressionLA.com
PsychiatryGuidelines.com

Depression Treatment
- **Context**
- **Diagnosis**
- **Acute Treatment**
  focus on stabilization, remission, & recovery for treatment selection & monitoring
- **Long-term Management Strategies**
  focus on remaining well in the face of a chronic illness

The Context: Why is this so important to treat?

- High Prevalence
- Societal Cost
- Health Consequences

Prevalence of Major Depression
- In any year ~10% of American adults experience depression (~19M individuals)
- Nearly 1 in 6 adults will have MDD during their lifetimes
  - 10% - 25% of women
  - 5% - 12% of men
- Complicated by Dysthymic Disorder
  - 25% of MDD patients have “double depression” i.e. recurrent depressions without full recovery between episodes.

Regier, Arch Gen Psychiatry, 1993
Costs of Depression

Total costs in the US in 2003 ~ $83 billion
Total NIH Budget (FY2005) ~ $29B
Total California Budget (2005-6) ~$90B
Total GNP of New Zealand (2004) ~$82B


Global Burden of Disease

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>% Total</th>
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<tbody>
<tr>
<td>1</td>
<td>Ischemic heart disease</td>
<td>5.9</td>
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<tr>
<td>2</td>
<td>Unipolar major depression</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>Road traffic accidents</td>
<td>5.1</td>
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<tr>
<td>4</td>
<td>Cerebrovascular disease</td>
<td>4.4</td>
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<td>5</td>
<td>Chronic obstructive pulmonary disease</td>
<td>4.2</td>
</tr>
<tr>
<td>6</td>
<td>Lower respiratory infections</td>
<td>3.1</td>
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<tr>
<td>7</td>
<td>Tuberculosis</td>
<td>3.0</td>
</tr>
<tr>
<td>8</td>
<td>War injuries</td>
<td>3.0</td>
</tr>
<tr>
<td>9</td>
<td>Diarrheal diseases</td>
<td>2.7</td>
</tr>
<tr>
<td>10</td>
<td>HIV</td>
<td>2.6</td>
</tr>
</tbody>
</table>


Mood as continuum

Depression  Dysthymia  Neutral  Hyperthymia  Euphoria
(Major Depression) (Mania)

Mood Disorders as Categories

Major Depressive Disorder (mild, moderate, severe, +/- psychotic features; single episode vs recurrent)
Dysthymic Disorder
Bipolar I (manic depression)
Bipolar II (depressions with hypomanias)
Cyclothymia (bidirectional swings of lesser severity)
Depressions: Diagnostic Features

- **Mood Symptoms**
  - Sad or depressed mood; loss of interest or pleasure in activities (anhedonia)
- **Neurovegetative Symptoms**
  - Sleep disturbance; appetite/weight changes; agitation or psychomotor slowing; fatigue
- **Cognitive Symptoms**
  - Diminished concentration or indecisiveness; excessive guilt & worthlessness; suicidal ideation or thoughts of death

Reformatted from DSM-IV-TR

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Info to elicit in your interview

- Chief complaint & why seek care now?
- Which of the 9 DSM-IV criteria for a major depressive episode are present / duration?
- Family history of neuropsychiatric illnesses
- Past personal treatment history (ATHF)
- Comorbidities (medical and psychiatric)
- Level of function / disability
- First episode or a recurrence
- Suicidality - present and past
- Social supports (or lack thereof)

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Initial Acute Management: focus on stabilization on the way to remission

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Course During Treatment

- Asymptomatic
- Depressive Symptoms
- Depressive Syndrome

Major Serotonergic Agents (reuptake transporter inhibitors)

- **Fluoxetine** (Prozac, Sarafem - Lilly)
- **Sertraline** (Zoloft - Pfizer)
- **Paroxetine** (Paxil - GlaxoSmithKline)
- **Fluvoxamine** (Luvox - Solvay)
- **Citalopram** (Celexa - Forest)
- **Escitalopram** (Lexapro - Forest)

* Available as generic
**Mixed Activity Agents**  
*Serotonin and Norepinephrine*

- **Venlafaxine** *(Effexor - Wyeth)*
- **Trazodone** *(Desyrel - BMS)*
- **Mirtazapine** *(Remeron - Organon)*
  - Antagonist @ presynaptic alpha2-adrenergic receptor
  - Postsynaptic 5-HT\(_2\) and 5-HT\(_3\) receptors
- **Duloxetine** *(Cymbalta - Lilly)*

* Available as generic

**Significantly Noradrenergic**

- **Desipramine** *(Norpramine / Hoechst )*
- **Nortriptyline** *(Pamelor / Sandoz )*
- **Reboxetine** *(Vestra? Pharmacia/Pfizer) - not in US*

* Available as generic

**Dopaminergic Agents**

- **Bupropion** *(Wellbutrin, Zyban - GSK)*
- **Venlafaxine** at high doses (>225mg/d)
- **Psychostimulants** *(medically-ill inpts)*

* Available as generic

**Pharmacologic Effects of Antidepressants**

- Reduce depression
- Psychomotor activation
- Antiparkinsonian effects
- Sedation
- Euphoria
- Weight gain
- Sexual dysfunction
- GI disturbances
- Antianxiety effects
- Sexual dysfunction
- Sedation

- Reduce depression
- Hypotension
- Antipsychotic effects
- Hypotension
- Sexual dysfunction
- GI disturbances
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**Potency and Affinity**

- **Affinity** - an attraction between molecules that brings them together (inverse of the dissociation constant) (e.g. a receptor and its ligand)
  - High affinity - binds tightly
- **Potency** - how much of the drug is needed to achieve a particular effect (e.g. inhibit reuptake in 50% of the transporters)
  - High potency - few moles/milligrams

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**Estimated Binding Affinities (Kᵢ) of Antidepressants for Monoamine Transporters**

<table>
<thead>
<tr>
<th></th>
<th>SERT</th>
<th>NET</th>
<th>Kᵢ Ratio</th>
<th>Log Ratio</th>
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<tbody>
<tr>
<td>Desipramine</td>
<td>163</td>
<td>3.5</td>
<td>0.02</td>
<td>-1.67</td>
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<tr>
<td>Nortriptyline</td>
<td>18</td>
<td>1.49</td>
<td>0.08</td>
<td>-1.08</td>
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<tr>
<td>Nefazodone</td>
<td>549</td>
<td>713</td>
<td>1.30</td>
<td>0.11</td>
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<td>Imipramine</td>
<td>20</td>
<td>142</td>
<td>7.10</td>
<td>0.85</td>
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<tr>
<td>Duloxetine</td>
<td>0.8</td>
<td>7.5</td>
<td>9.38</td>
<td>0.97</td>
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<tr>
<td>Venlafaxine</td>
<td>102</td>
<td>1644</td>
<td>16.1</td>
<td>1.21</td>
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<td>Fluoxetine</td>
<td>20</td>
<td>2186</td>
<td>109.3</td>
<td>2.04</td>
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<td>Paroxetine</td>
<td>0.83</td>
<td>328</td>
<td>395.2</td>
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<tr>
<td>Sertraline</td>
<td>3.3</td>
<td>1716</td>
<td>520.0</td>
<td>2.72</td>
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<tr>
<td>Citalopram</td>
<td>1.13</td>
<td>4870</td>
<td>4310</td>
<td>3.63</td>
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</table>

Kᵢ = inhibition constant, nmol/L
Owens MJ J Pharmacol Exp Ther 1997; Bymaster Neuropsychopharmacol 2001; Vaishnavi Biol Psychiatry 2004

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**The Evolving Molecular Story**

- Other molecules beyond 5-HT, NE, and DA likely play a role in MDD & treatment (this is not for the PRITE)
- Neuropeptides
  - Substance P - neurokinin - pain & mood
  - Neuropeptide Y - response to stress
- HPA Axis Modulation
  - CRF antagonist - interrupt HPA cascade
  - Melanocyte stimulating hormone inhibitor
- Glutamate - excitatory neurotransmitter
  - NMDA antagonist, AMPA potentiator

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**Things to know about the management of depression, but not things to dwell upon in the ER**
Brain Stimulation I

• Electroconvulsive Therapy (ECT)
  • Often employed after other steps in the algorithm have failed
  • Despite this, it yields improvement in a high proportion of patients, often rapidly (1-2 wks)
  • Common side effects include transient memory disturbances, anesthesia concerns
  • Use in depression, mania, psychosis
  • Particular use in TRD, psychotic depression, pregnancy, other medical comorbidities

Brain Stimulation II

• Vagus Nerve Stimulation (VNS)
  • FDA granted approval for use as an adjunct to meds in TRD
  • Device is implanted in chest wall, electrodes tunneled to vagus nerve (usually left, in neck)
  • Therapeutic benefit appears to accrue over time
• Deep Brain Stimulation (DBS)
  • Stimulation of Brodmann Area 25 via implanted electrodes appears to produce rapid symptom improvement in TRD
  • Mostly case series evidence

Brain Stimulation III

• Transcranial Magnetic Stimulation
  • Induces a non-convulsive current in cortex
  • Used by neurologists to stimulate or inhibit ctx
  • Clinical trials have produced mixed results
• Transcranial Direct Current Stimulation
  • Extremely low energy direct current is passed between scalp electrodes (1 mA x 20 min 3x/wk)
  • Clinical trials report symptom improvement after stroke, in Huntington’s disease, in MDD
  • May promote neural plasticity?

Psychotherapy

• Strong evidence for “manualized” therapies, such as cognitive behavioral therapy, and specific modalities (e.g. “exposure”) in particular phobias
• Useful both as treatment by itself and in conjunction with pharmacotherapy
Psychotherapeutics

- Cognitive Behavioral Therapy*
- Interpersonal Therapy*
- Psychodynamic Psychotherapy*
- Supportive Psychotherapy
- Brief Psychotherapy
- In MDD, one should re-evaluate if there is not at least a moderate improvement by 4-8 weeks of treatment
- Newer Approaches
  - Mindfulness Based Cognitive Therapy
  - Problem Solving Treatment
  - Cognitive Behavioral Analysis System of Psychotherapy

* Noted in APA Practice Guideline 2000

Long-term Strategies for Patients with Depression:
a Chronic Illness Model

Implications of Targeting Response but Not Remission

Residual symptoms: HAM-D≥8

“Response”

“Remission”

HAM-D≤7

Risk of Recurrence

3-Point Dosing Strategy

• Titrate up to an effective dose
• Monitor for tolerability
• Maintenance dose = full effective dose (i.e. remission dose)

STAR*D Strategies

• Level 2
  • Switch - sertraline, venlafaxine, bupropion, CBT
  • Augment - buspirone, bupropion, CBT

• Level 3
  • Switch - mirtazapine, nortriptyline
  • Augment - lithium, thyroid hormone

• Level 4
  • Switch - tranylcypromine, mirtazapine + venlafaxine

Most recent publications are listed online on www.STAR-D.org

Lastly, a word from our Regulators

• 2004 - FDA issued a Public Health Advisory, indicating the need for close monitoring of all patients treated for depression; a Talk Paper focused on antidepressants in children; and recommendations from meetings of the Psychopharmacologic Drugs and Pediatric Advisory Committees included
  • that a “black box” warning of increased risk of suicidality in pediatric patients be applied to all antidepressant medications
  • that they not be contraindicated in pediatric patients
• Update in labeling for all antidepressants in 10/2004
• 2005 - New patient and healthcare info sheets became available; a PHA and a new Talk Paper reiterated that adult patients should be closely monitored for suicidal thoughts or behaviors.
• 2006 - Retrospective analysis suggested VLX overdoses may be more dangerous than SSRIs but less dangerous than TCAs; label change
• 2006 - present - Data from clinical trials continue to be studied.
• Preliminary STAR*D genetics data suggest specific variations in CREB1 may elevate risk of TESI in men (Perlis AGP 2007)

Antidepressant Class Labeling for Antidepressants and Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert established name] is not approved for use in pediatric patients. [This sentence would be revised to reflect if a drug were approved for a pediatric indication(s). Such as, [Insert established name] is not approved for use in pediatric patients except for patients with [Insert approved pediatric indication(s)].] (See Warnings and Precautions: Pediatric Use)